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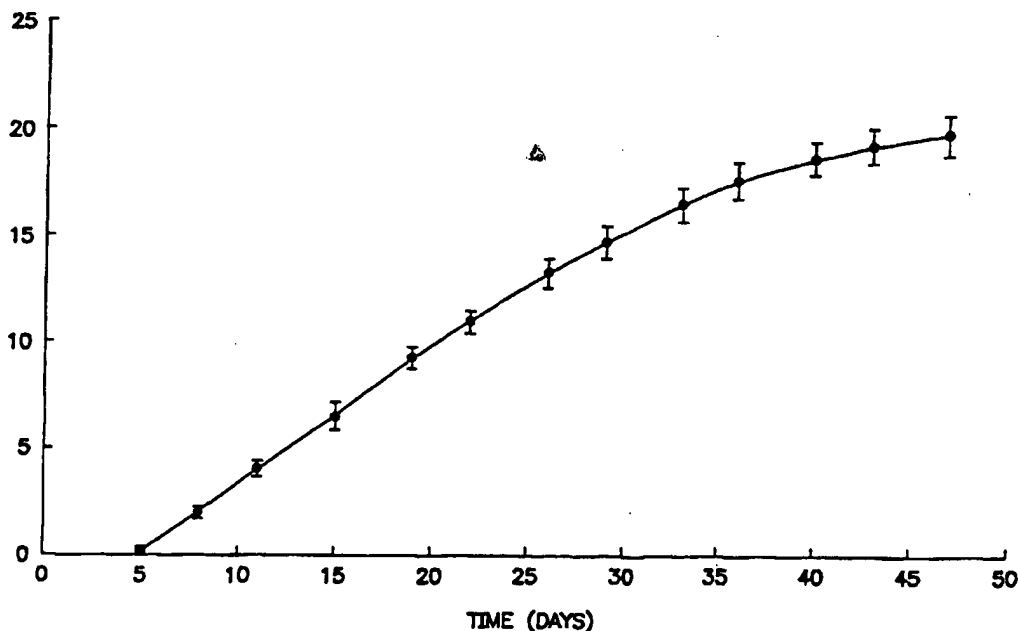
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(54) Title: PEPTIDE/PROTEIN SUSPENDED FORMULATIONS



(57) Abstract

The present invention provides improved compositions for improving the chemical and physical stability of peptides and proteins. The invention provides a liquid beneficial agent formulation containing a liquid suspension comprising at least 5 % by weight beneficial agent and having a viscosity and beneficial agent size which minimizes setting of the agent in suspension over the extended delivery period.

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## PEPTIDE/PROTEIN SUSPENDING FORMULATIONS

### TECHNICAL FIELD

This invention relates to stabilized, concentrated suspensions formulations of peptides and proteins. More particularly, this invention relates to novel and improved compositions for providing concentrated, non-aqueous suspensions of peptides/proteins for pharmaceutical use having adequate chemical, physical and bioactive stability suitable for long term delivery from a sustained release drug delivery system.

### BACKGROUND ART

Proteins, as well as many other biologically active compounds, degrade over time in aqueous solution. Because of this chemical instability, protein solutions are often not suitable for use in drug delivery devices. Carriers, in which proteins do not dissolve but rather are suspended, can often offer improved chemical stability. Furthermore, it can be beneficial to suspend the beneficial agent in a carrier when the agent exhibits low solubility in the desired vehicle. However, suspensions can have poor physical stability due to settling and agglomeration of the suspended beneficial agent. The problems with non-aqueous carriers tend to be exacerbated as the concentration of the active compound is increased.

For drug delivering implants, dosing durations of up to one year are not unusual. Beneficial agents which have low therapeutic delivery rates are prime candidates for use in implants. When the device is implanted or stored, settling of the beneficial agent in the liquid formulation can occur. This heterogeneity can adversely effect the concentration of the beneficial agent dispensed. Compounding this problem is the size of the implanted beneficial agent reservoir. Implant reservoirs are generally on the order of

1 25-250  $\mu$ l. With this volume restriction, a formulation of high concentration  
2 (greater than or equal to 10%) and a minimum amount of suspension vehicle  
3 and other excipients is preferred.

4 Alpha interferon ( $\alpha$ -IFN) is one example of a beneficial agent which  
5 provides a therapeutic effect at a low dose. This interferon is indicated in the  
6 treatment of chronic hepatitis because of its antiviral activity. Prescribed  
7 therapy presently entails injections of  $\alpha$ -IFN solution, containing about  
8  $3.0 \times 10^6$  IU (15 micrograms) of agent per dose, three times per week for a  
9 4 to 6 month period. Frequent injections are required because of the short  
10 elimination half-life of  $\alpha$ -IFN; most of the drug being completely cleared from  
11 the plasma within eight to ten hours after the injection.

12 U.S. Pat. Nos. 4,871,538 issued to Yim et al; 4,847,079 issued to  
13 Kwan et al; 5,081,156 issued to Yamashira et al, and European Publication  
14 No. 0,281,299 issued to Yim et al describe IFN /peptide compositions with  
15 concentrations between  $10^4$  to  $10^8$  IU/ml. In Kwan et al, a pharmaceutical  
16 solution having a  $\alpha$ -IFN concentration of  $10^3$  to  $10^8$  IU/ml is described.  
17 Yim describes a dosage range being between  $10^4$  to  $10^8$  IU  $\alpha$ -IFN/ml.  
18 In Yim II, an insoluble complex including  $\alpha$ -IFN, zinc, and protamine is  
19 suspended in a phosphate buffer. Yim I, Yim II, and Kwan, however, teach  
20 the use, in part, of an aqueous buffer in their compositions. This leads to  
21 possible hydrolysis of the compound, leading to chemical degradation and  
22 instability. Yamashira teaches a sustained release preparation of interferon in  
23 a mixture with a biodegradable carrier. IFN is incorporated at concentrations  
24 of  $10^3$  to  $10^8$  IU per 1 mg of carrier or, alternatively, each dosage form  
25 containing  $10^4$  to  $10^8$  IU of interferon. Furthermore, while the patents and  
26 publications described above describe concentrations between  $10^4$  to  $10^8$   
27 IU/ml, none describe concentrations on the order of  $10^9$  to  $10^{11}$  IU/ml.

1           There is a need for a novel composition comprising a nonaqueous  
2           suspension vehicle and concentrated protein/peptide as the beneficial agent  
3           for use in implanted, sustained release devices. While it is known in the art to  
4           achieve stable  $\alpha$  IFN concentrations of up to  $10^8$  IU/ml, this invention utilizes a  
5           novel combination whose combined effect produces a significant and  
6           surprising improvement in the physical and chemical stability of the beneficial  
7           agent compound over other formulations.

#### 8 9                           BRIEF DESCRIPTION OF THE DRAWINGS

10  
11           FIG. 1 is a cross-section of an implantable sustained release osmotic  
12           delivery device for use in combination with the concentrated suspensions of  
13           the present invention.

14           FIG. 2 is a graph illustrating the stability of a cytochrome c suspension.

15           FIG. 3 is a graph illustrating the stability of an  $\alpha$ -interferon suspension.

#### 16 17                           DESCRIPTION OF THE INVENTION

18  
19           One aspect of this invention relates to preparations for stabilizing  
20           peptides and proteins at high concentrations for extended periods of time.

21           Another aspect of this invention relates to stabilized preparations of  
22           human  $\alpha$ -IFN.

23           Another aspect of this invention relates to stabilized preparations of  
24           human  $\alpha$ -IFN having concentrations of at least  $1 \times 10^9$  IU/ml.

25           Another aspect of this invention relates to stabilizing beneficial agent  
26           formulations comprising a beneficial agent having a particle size of between  
27           0.3 to 50 microns and suspension vehicle formula having a viscosity between  
28           100 to 100,000 poise at 37°C.

1           The new formulations are physically stable suspensions which provide  
2 chemical stability to water sensitive compounds and can be employed to  
3 stabilize high concentrations of the active compound. The carrier  
4 components are acceptable for use in implantable systems.

5

6                           MODES FOR CARRYING OUT THE INVENTION

7

8           The concentrated beneficial agent suspensions of the present  
9 invention provide significantly stable concentrations over extended periods of  
10 time, useful for sustained delivery, implant applications. The suspensions of  
11 this invention minimize the particle degradation due to hydrolysis and particle  
12 settling over the duration of the extended delivery period. These extended  
13 periods of time are between one week to two years, preferably between three  
14 months to one year.

15           The sustained parenteral delivery of drugs provides many advantages.

16           Typical sustained release implantable osmotic delivery devices are  
17 described in U.S. Pat. Nos. 5,034,229; 5,057,318; and 5,110,596 which are  
18 incorporated herein by reference. As shown in Fig. 1, these devices 10  
19 typically comprise a housing 12 including a fluid impermeable wall section 14  
20 and a fluid permeable wall section 6 which sections define and surround an  
21 internal compartment 18. An exit passageway 20 is formed within the fluid  
22 impermeable wall section to fluidly communicate the internal compartment 18  
23 with the external environment. To minimize exposure to the environmental  
24 fluids, a beneficial agent 22 is contained within the fluid impermeable section.

25           An expandable driving member 24, contained within the fluid permeable  
26 section, expands with the imbibition of fluid across the fluid permeable wall  
27 section. Typically a piston 26 separates the beneficial agent 22 from the  
28 expandable driving member 24. This forces the agent out through the exit

1 passageway and into the environment of use. The non-aqueous  
2 administration of a beneficial agent in the suspension formulation as  
3 disclosed herein can be accomplished using implant devices of these kinds.

4 According to this invention, high concentrations of the beneficial agent  
5 remain suspended, and physically and chemically stable in a non-aqueous  
6 suspension vehicle. "High concentration" is defined as the beneficial agent  
7 concentration level of at least about 0.5 wt% of the formulation, preferably  
8 at least about 5 wt% and most preferably between about 10 to 70% w/w.  
9 For example, "high concentrations" of  $\alpha$ -IFN are  $10^9$  to  $10^{11}$  IU; and for  
10 salmon calcitonin, concentrations of between  $2 \times 10^4$  IU to  $2.8 \times 10^6$  IU  
11 are "high concentrations". The beneficial agent particle size is between  
12 0.3 to 50 microns, and preferably about 1-10 microns in diameter. Desired  
13 particle size can be provided typically by milling, sieving, spray drying,  
14 supercritical fluid extraction of the particular beneficial agent selected.  
15 Typical beneficial agents for use in this device and composition include the  
16 interferons and calcitonin. Other representative beneficial agents that can be  
17 administered include pharmacologically active peptides and proteins, anabolic  
18 hormones, growth promoting hormones, hormones related to the endocrine  
19 system comprising porcine growth promoting hormone, bovine growth  
20 promoting hormone, equine growth promoting hormone, ovine growth  
21 promoting hormone, human growth promoting hormone, growth promoting  
22 hormones derived by extraction and concentration from pituitary and  
23 hypothalamus glands, growth promoting hormones produced by recombinant  
24 DNA methods, bovine growth promoting hormone as described in Nucleic  
25 Acid Res., Vol. 10, p 7197 (1982), ovine growth promoting hormone as  
26 described in Arch. Biochem. Biophys., Vol. 156, p 493 (1973), and porcine  
27 growth promoting hormone as described in DNA, Vol. 2, pp 37, 45, (1983).  
28 Representative beneficial agents also comprise cochicine, cosyntropin,  
29 and lypressin. The polypeptides also comprise growth hormone, somatropin,  
30 somatotropin, somatotropin analogues, modified porcine somatotropin,

1 modified bovine somatotropin, derivatives of both porcine and bovine  
2 somatotropin, somatomedin-C, gonadotropic releasing hormone, follicle  
3 stimulating hormone, luteinizing hormone, LH-RH, LH-RH analogs, growth  
4 hormone releasing factor, gonadotropin releasing factor, insulin, chorionic  
5 gonadotropin, oxytocin, somatotropin plus an amino acid, vasopressin,  
6 adrenocorticotrophic hormone, epidermal growth factor, prolactin,  
7 somatostatin, somatotropin plus a protein, polypeptides such as thyrotropin  
8 releasing hormone, thyroid stimulating hormone, secretin, pancreozymin,  
9 enkephalin, glucagon, endocrine agents secreted internally and distributed in  
10 an animal by way of the bloodstream, and the like. The beneficial agents and  
11 their dosage unit amounts are known to the prior art in The Pharmacological  
12 Basis of Therapeutics, by Gilman, Goodman, Rall and Murad, 7th Ed., (1985)  
13 published by MacMillan Publishing Co., NY; in Pharmaceutical Sciences,  
14 Remington, 17th Ed., (1985) published by Mack Publishing Co., Easton, PA,  
15 and in U.S. Pat. No. 4,526,938. Particularly preferred are beneficial agents  
16 which produce the desired therapeutic effect at a low delivery rate/dose,  
17 for example, proteins/peptides which require picograms to milligrams of  
18 agent.

19 A pharmaceutically acceptable suspension vehicle is used to suspend  
20 the solid beneficial agent particles in the beneficial agent formulation.  
21 Non-aqueous vehicles are used to isolate the beneficial agent from water and  
22 prevent hydrolysis or other degradation of the beneficial agent while in  
23 suspension. Furthermore, pharmaceutically acceptable suspension vehicles  
24 may function as a thickening agent for the components present in an implant.  
25 As a vehicle for transporting beneficial agents from the implant, it provides  
26 protection against the decomposition of a beneficial agent, and it imparts  
27 physical and chemical stability to components present in the formulation.  
28 The thickening agent may be used to increase the viscosity of the formulation  
29 to prevent fluids in the implantation environment from mixing with the



1 implant's beneficial agent formulation. The amount of thickening agent  
2 present in the formulation is between 1% to 99.9% and preferably 5-60%  
3 depending upon the viscosity adjustment needed.

4 Typical non-aqueous suspension vehicles include: waxes, which have  
5 a softening temperature at or less than body temperature; hydrogenated  
6 vegetable oils, (e.g., peanut oil, cottonseed oil, sesame oil, castor oil, olive oil,  
7 corn oil, iodinated poppy seed oils) silicon oil, medium chain fatty acid  
8 monoglycerides, or polyols. Of these polyols are preferred.

9 Polyols suitable for suspension vehicles include such as diol, triol,  
10 polyhydric alcohol, and the like. More specific polyols comprise polyethylene  
11 glycol (average molecular weight between 200 and 1000), propylene glycol,  
12 polyethylene glycol 1,5-pentylene glycol; 1,6-hexylene glycol; 1,7-heptylene  
13 glycol; 1,9-nonylene glycol; 1,2-dimethyl-1,6-hexylene glycol;  
14 1,2,3-propanetriol; 1,2,5-pentanetriol; 1,3,5-pentanetriol; 1,2,4-butanetriol;  
15 dipentaerythriol, and the like. In another embodiment the pharmaceutically  
16 acceptable suspension vehicle comprises glycerol mono(lower alkyl) ethers  
17 and glycerol di(lower alkyl) ethers such as glycerol 1-methyl ether; glycerol  
18 1-ethyl ether; glycerol 1,2-dimethyl ether; glycerol 1,3-dimethyl ether,  
19 and the like. In another embodiment the pharmaceutically acceptable vehicle  
20 comprises a mixture such as propylene glycol and glycerol, and the like.

21 Sufficient viscosity is required to suspend the particles in the carrier  
22 throughout the duration of the extended delivery period. Settling is a function  
23 of the particle size and the carrier viscosity. If the duration of the delivery  
24 period is shorter, the viscosity can be lower since the time required to be

1   suspended is shorter. The viscosity required, for example, can be determined  
2   by the Stokes-Einstein equation which is a measure of how far a particle in  
3   suspension will travel

$$V = \frac{2gR^2 (P_p - P_c)}{9\mu}$$

4  
5  
6  
7  
8  
9       V   = velocity of settling  
10      μ   = viscosity of the carrier  
11      g   = acceleration due to gravity  
12      P<sub>p</sub> = density of particle  
13      P<sub>c</sub> = density of carrier

14  
15   wherein R = the average particle radius of the beneficial agent. The viscosity  
16   of the beneficial agent suspending formulation can be altered by the use of  
17   thickening agents to raise the viscosity to the desired level. Typical  
18   thickening agents for use in the compositions of this invention include suitable  
19   hydrogels such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose  
20   (HPMC), sodium carboxymethyl cellulose, polyacrylic acid, poly(methyl  
21   methacrylic acid) (PMMA). Preferred hydrogels are cellulose ethers such as  
22   hydroxyalkylcellulose and hydroxyalkylalkyl-cellulose compounds. A most  
23   preferred hydroxyalkylcellulose is hydroxypropyl cellulose (HPC) and  
24   povidone (PVP). Hydroxypropyl cellulose is commercially available in a wide  
25   range of viscosity grades sold under the tradename Klucel™ (Hercules, Ltd.,  
26   London, England). The concentration of the hydroxyalkylcellulose is  
27   dependent upon the particular viscosity grade used and the desired viscosity  
28   of the liquid composition. For example, where the desired viscosity is less  
29   than about 1000 poise (cps), hydroxypropyl cellulose having an average  
30   molecular weight of about 60,000 daltons (i.e., Klucel EF™) can be used.  
31   Where the desired viscosity is from about 1000 to about 2500 cps, higher  
32   viscosity grades of hydroxypropyl cellulose can be used (i.e., Klucel LF™ and  
33   Lucel GF™). In addition to using different viscosities of different thickening

1 agents, using different amounts of the same particular thickening agent can  
2 be used to vary the viscosity. Preferably, the concentration of hydroxypropyl  
3 cellulose is from 5 percent w/w and, more preferably from 5 to 20 %w/w of the  
4 carrier and most preferably between 8-18 %w/w. Aluminum monostearate  
5 can be used as a thickening agent if oils are used as the carrier.

6 Hydroxyalkylalkylcellulose ethers are a class of water-soluble  
7 hydrogels derived from etherification of cellulose. As used herein in reference  
8 to this class of hydrogels, the term "alkyl" means C<sub>1</sub>-C<sub>6</sub> alkyl where alkyl  
9 refers to linear or branched chains having 1 to 6 carbon atoms, which can be  
10 optionally substituted as herein defined. Representative alkyl groups include  
11 methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like.

12 Exemplary hydroxyalkylalkylcelluloses are hydroxypropylmethyl  
13 cellulose, hydroxyethylmethyl cellulose and hydroxybutylmethyl cellulose.  
14 Hydroxypropylmethyl cellulose (HPMC) is preferred. HPMC is commercially  
15 available (i.e., Aldrich Chem. Co., Ltd. Dorset, England and Dow Chem. Co.,  
16 Midland, Mich., USA) in a wide range of viscosity grades. In addition to  
17 increasing viscosity, hydroxyalkylalkylcelluloses can serve as a stabilizing,  
18 suspending and emulsifying agent. The concentration of  
19 hydroxyalkylalkylcellulose in a liquid composition of this invention is  
20 dependent inter alia on its intended use (i.e., stabilizer, emulsifier,  
21 viscosity-increasing agent) and its viscosity grade.

22 To assure the viscosity of the suspension vehicle is sufficient to  
23 maintain the agent in suspension over the desired delivery period, thickening  
24 agents can be added to the suspension vehicle. The preferred thickening  
25 agents include povidone and hydroxypropyl cellulose. In one embodiment,  
26 when the PEG utilized is a low molecular weight, e.g., 400, 5% hydroxypropyl  
27 cellulose, having an average molecular weight of 1000, or 40 -60% povidone  
28 can be used in combination with a balance of polyethylene glycol. If the

1 polyethylene glycol utilized in the suspension vehicle has a molecular weight  
2 of greater than 600, e.g., 1000 molecular weight, povidone is preferably  
3 utilized as the thickening agent.

4 The following examples are offered to illustrate the practice of the  
5 present invention and are not intended to limit the invention in any manner.

6

7

#### EXAMPLE 1

8

9 A viscous carrier was prepared containing 50% PEG 400 and  
10 50% povidone (PVP) by weight. PEG 400 (Union Carbide) was weighed  
11 into a beaker and an equal weight of povidone K29-32 (GAF) was added.  
12 The PEG and povidone were mixed by stirring with a spatula for about  
13 5 minutes. The blended carrier was allowed to sit overnight to insure  
14 complete dissolution of the povidone. The carrier was then deaerated in a  
15 vacuum oven (National Appliance Company) by drawing a vacuum and  
16 holding the carrier at 50°C for 30 minutes.

17 Cytochrome c (Sigma, from horseheart) was milled in a jar mill and  
18 then passed through a 400 mesh screen to produce a particle diameter of  
19 less than 37 micron. In a beaker, 0.5566 grams of the cytochrome c was  
20 added to 4.9970 grams of the PEG 400/povidone carrier to prepare a 10%  
21 cytochrome c suspension in 50:50 PVP:PEG 400 carrier. The suspension  
22 was thoroughly blended by mixing with a spatula for about 5 minutes.  
23 The cytochrome c suspension was then loaded into 11 osmotic veterinary  
24 implants (as in Figure 1).

25 The implants were tested in vitro by releasing into culture tubes filled  
26 with deionized water. To monitor release of cytochrome c from the implants,  
27 samples of the release media were assayed on a UV spectrophotometer  
28 (Shimadzu UV 160U) at a wavelength of 409 nm. The implants delivered the  
29 cytochrome c successfully over the designed duration of the implant

1 (42 days). Fig. 2 is a graph that illustrates the cumulative protein delivery  
2 (mg) over time. During the later half of the release period, several implants  
3 were removed from the tubes and examined to determine whether settling of  
4 the cytochrome c had occurred. These implants were sectioned and samples  
5 of the protein suspension were removed from the top and bottom portions of  
6 the implant. The samples of the protein suspension were weighed, diluted  
7 with DI water in volumetric flasks and assayed via UV a spectrophotometer.  
8 Results indicated that the cytochrome c suspension was homogeneous.

9

10

## EXAMPLE 2

11

12 Standard : 20  $\mu$ l of a 8.0 mg/ml standard was diluted to 160  $\mu$ g/ml.

13 Each HPLC sample was diluted by a factor of 10 into distilled water.

14 The operating conditions of the HPLC were as follows:

15 Column: POROS RH 2.1 mm x 3.0 cm

16 Mobile phase: A: 95% H<sub>2</sub>O, 0.1% TFA, 5% ACN

17 B: 95% ACN, 5% H<sub>2</sub>O, 0.083% TFA

18 Gradient: 20% B to 50% B in 5 minutes

19 Flow: 2.0 ml/min

20 Detector: 280 nm @ 0.002 AUFS

21 IRMA Standards: Working standards were prepared by diluting IRMA  
22 standards into phosphate buffered saline (PBS) containing 0.5% Bovine  
23 Serum Albumin (BSA). Samples were prepared by serially diluting by factors  
24 of 400 for interferon formulations and 2000 for the standard into PBS  
25 containing 0.5% BSA.

26 Figure 3 shows the results of the HPLC and the IRMA assays.

27 The HPLC measurements indicate no losses of the  $\alpha$ -IFN over 5 days, even  
28 at 37° C, indicating stability of this protein in non-aqueous vehicle. Relative  
29 to the initial stock solution, the activity shown by IRMA at  $t = 0$  is 78%.

1 At t = 5 days, the formulation displayed an activity of 87% at room  
2 temperature and 90% at 37°C. When compared to the original stock,  
3 no losses of  $\alpha$ -IFN were detected by HPLC in this formulation. Stability  
4 of interferon in PEG over 5 days at 37° C was indicated by this assay.  
5 However, approximately 80 - 90% of the activity of the initial stock was  
6 maintained. The IRMA readings suggest no activity losses due to time and  
7 temperature effects.

8 This invention has been described in detail with particular reference  
9 to certain preferred embodiments thereof, but it will be understood that  
10 variations and modifications can be effected within the spirit and scope of  
11 the invention.

1    WHAT IS CLAIMED IS:

2

3           1.     A beneficial agent formulation for use in a device which delivers  
4     the formulation over an extended delivery period, the formulation comprising  
5     a suspension containing at least 5% by weight beneficial agent in the form of  
6     solid particles, the beneficial agent particle size being 0.3 to 50 microns and  
7     the suspension viscosity being sufficient to prevent settling of the agent in the  
8     suspension formulation over the extended delivery period.

9           2.     The formulation of claim 1, wherein the particle size is between  
10    1 to 10 microns.

11          3.     The formulation of claim 1, wherein the viscosity is 100 to  
12    100,000 poise at 37°C.

13          4.     The formulation of claim 1, wherein the extended delivery period  
14    is at least about 1 month.

15          5.     The formulation of claim 1, wherein the liquid suspension  
16    further comprises a low molecular weight polyol and a thickening agent.

17          6.     The formulation of claim 5, wherein the polyol is polyethylene  
18    glycol having a molecular weight between 200 and 1000.

19          7.     The formulation of claim 6, wherein the thickening agent  
20    comprises povidone.

21          8.     The formulation of claim 5, wherein the polyol is polyethylene  
22    glycol having a molecular weight between 200 and 600.

23          9.     The formulation of claim 8, wherein the thickening agent  
24    comprises povidone or hydroxypropyl cellulose.

25          10.    The formulation of claim 1, wherein the beneficial agent is  
26    human  $\alpha$ -interferon.

27          11.    The formulation of claim 10, wherein the concentration of  
28    interferon is at least  $1 \times 10^9$  IU.

29          12.    The formulation of claim 1, wherein said beneficial agent is a  
30    water sensitive compound.

1           13.    A beneficial agent delivery device containing the formulation of  
2    claim 1.

3           14.    The beneficial agent delivery device of claim 13, wherein the  
4    device is adapted to be implanted within an animal.

5           15.    A composition for sustained controlled delivery over an  
6    extended delivery period, the composition comprising:

7           (a)    0.5% to 70% by weight beneficial agent having a particle size of  
8                   between 0.3 to 50 microns; and

9           (b)    a non-aqueous liquid suspension formulation characterized by a  
10   viscosity of between 100 to 100,000 poise at 37 ° C, the formulation further  
11   comprising polyethylene glycol with a molecular weight between 200 and  
12   1000 and a thickening agent.

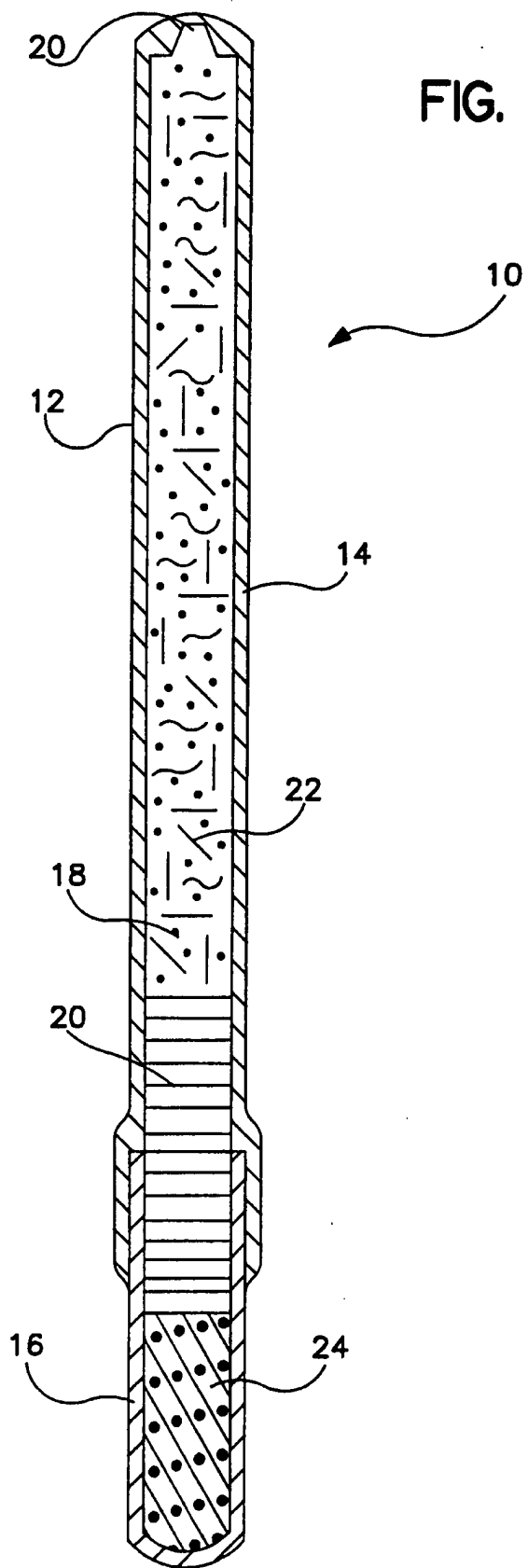
13          16.    The composition according to claim 15, wherein the thickening  
14   agent comprises povidone or hydroxypropyl cellulose.

15          17.    A beneficial agent delivery device containing the composition of  
16   claim 15.

17          18.    The beneficial agent delivery device of claim 17, wherein the  
18   device is adapted to be implanted within an animal.

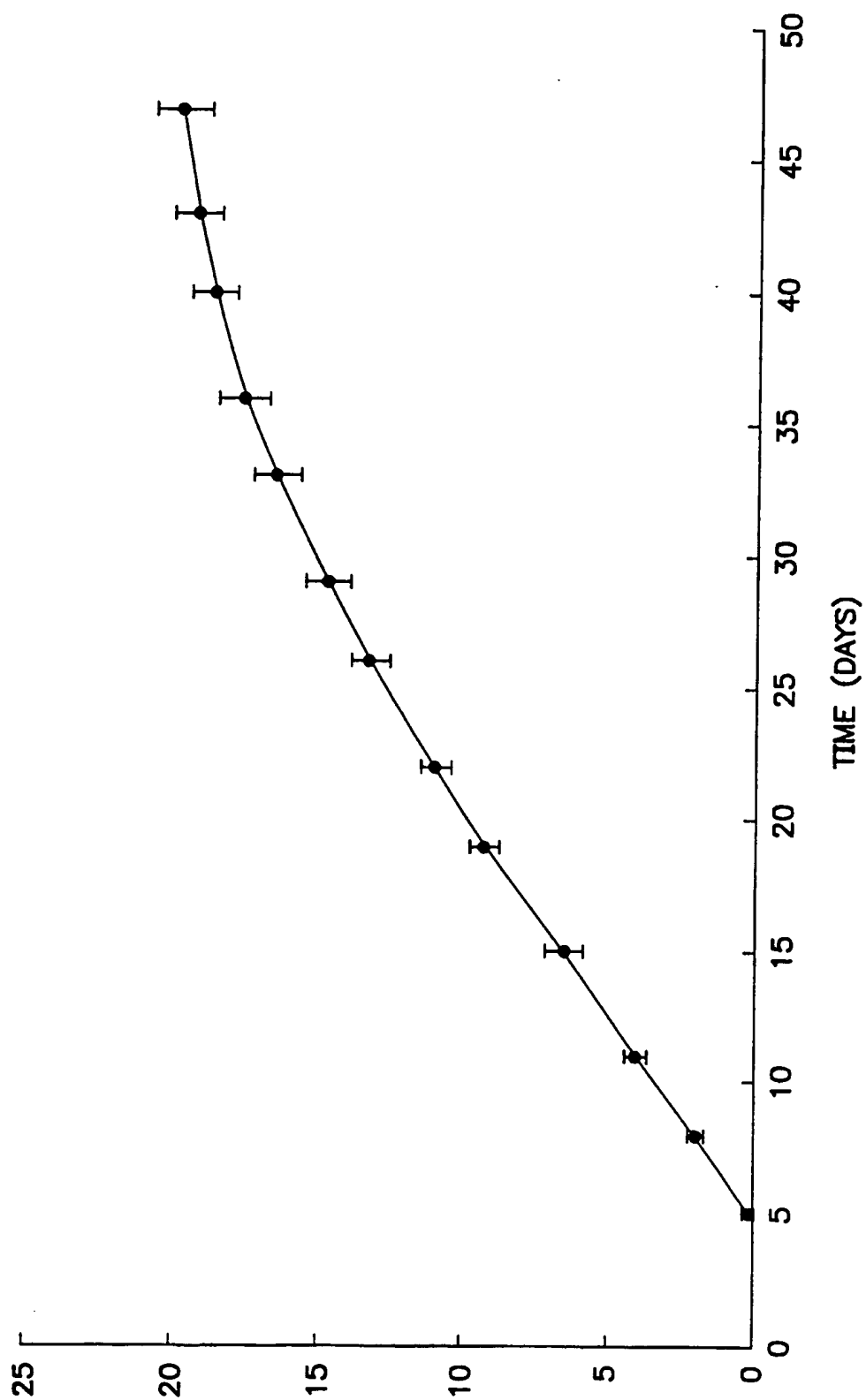


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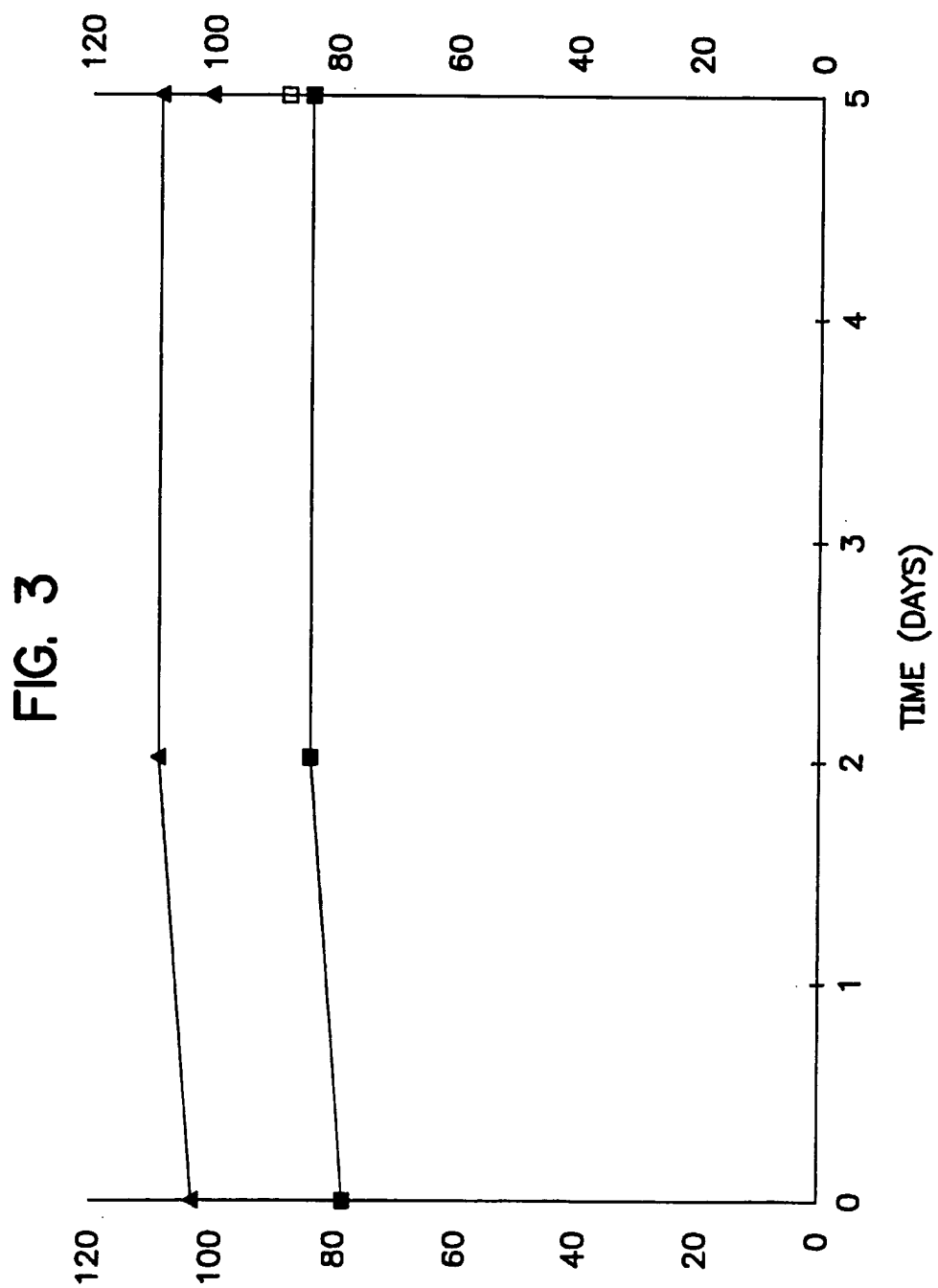


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FIG. 2



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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/07377

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00 A61K47/10 A61K47/32 A61K47/38

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 374 120 (MONSANTO COMPANY) 20 June 1990	1,3,4, 12-14 10
Y	see claims 1,7,8 see page 6, line 54 - page 7, line 3 see page 7, column 19 - column 21 see page 7, column 38 - column 40 see page 7, column 50 - column 52 ---	
X	US,A,4 855 141 (ALZA CORPORATION) 8 August 1989 see claim 1 see column 10, line 22 - column 11, line 15 ---	1,5,12, 13
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "&" document member of the same patent family

Date of the actual completion of the international search

17 September 1996

Date of mailing of the international search report

30.09.96

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Ventura Amat, A

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/US 96/07377

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,Y	WO,A,95 34285 (ALZA CORPORATION) 21 December 1995 see claims 1,2 see page 14, line 20 - page 16, line 2 see page 20, line 3 - line 11 -----	10
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 96/07377

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US-A-4855141	08-08-89	AR-A- 240398 AU-A- 3012189 CA-A- 1337038 DE-T- 68907769 EP-A- 0337613 IE-B- 61335 JP-A- 1299568 NO-B- 177887 PT-B- 90074 US-A- 4959218 US-A- 4996060	30-04-90 28-09-89 19-09-95 04-11-93 18-10-89 02-11-94 04-12-89 04-09-95 31-03-94 25-09-90 26-02-91
WO-A-9534285	21-12-95	AU-A- 7108094	05-01-96